Racial Influence on Biochemical Disease-Free Survival in Men Treated with External-Beam Radiotherapy for Localized Prostate Cancer

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Background: We retrospectively analyzed the clinical characteristics and outcomes of various racial and ethnic groups who underwent radiotherapy alone for localized or locally advanced prostate cancer.

Methods: From April 1987 to January 1998, 964 patients underwent full-dose, external-beam radiotherapy alone for localized or locally advanced prostate cancer and were included in the study. The patients' medical records were reviewed for pertinent information.

Results: Of the 964 patients, 810 were non-Hispanic white, 86 were African-American, 54 were Hispanic, and 14 were Asian. The most significant difference between groups was in the proportion of patients who presented with initial PSA levels >20 ng/ml. More than 20% of men in all minority groups presented with a serum PSA >20 ng/ml, compared to only 11% of whites (p=0.0012). Similarly, 14% of minorities presented with Gleason scores ≥8 compared to only 11% of whites (p=0.0265). Hispanic and Asian patients exhibited a higher incidence of Gleason score ≥8 prostate cancer. When comparing the time intervals of 1995–1998 vs. 1987–1994, the number of men presenting for EBRT with PSA levels <10 ng/ml increased to 74% from 57% for Caucasians (p<0,001), 71% from 40% for African Americans (p=0.012), 67% from 49% for Hispanics (p=0.118), and no change (50%) for Asians.

Conclusions: The number of African-American patients presenting with favorable characteristics (PSA <10 ng/ml) is increasing. These findings suggest that the message of screening and early detection may be reaching the African-American community. Continued diligence in screening and early detection may improve prostate cancer outcome for other minority populations.

Key words: radiotherapy ■ prostate cancer ■ race

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INTRODUCTION

African-American men have a 47% higher incidence of prostate cancer than do white men in the United States.[1-3] Furthermore, compared to white men, African-American men are diagnosed with prostate cancer at a younger age[2,4] and tend to have not only higher-grade disease[2,5,6] but also higher-stage disease.[2,4,7,8] However, only one study, a surgical series of over 1,500 patients, has demonstrated race to be a prognostic factor in patients with organ-confined prostate cancer.[5] The preponderance of the data in patients treated by watchful waiting, surgery, or radiotherapy demonstrated race not to be a prognostic factor.[9-13] Similarly, previous data from our institution on prostate cancer patients treated by radiotherapy with or without adjuvant androgen ablation demonstrated that when patients are stratified by known pretreatment prognostic factors, the outcome for both African-American and white men is similar.[14] However, questions still abound as to whether race or ethnicity is an independent prognostic factor for outcome in patients receiving definitive radiotherapy. Our objective was to retrospectively analyze the clinical characteristics and outcomes of white, African-American, Hispanic, and Asian men who underwent radiotherapy alone for localized or locally advanced prostate cancer at The University of Texas M.D. Anderson Cancer Center.

PATIENTS AND METHODS

Patients

A database search identified 1,006 patients who underwent full-dose, external-beam radiotherapy alone for localized or locally advanced prostate cancer at M.D. Anderson Cancer Center from April 1987 to January 1998. Forty-two patients were excluded from our study because of insufficient follow-up (<12 months), leaving a total of 964 patients for analysis. No patient received neoadjuvant or adjuvant therapy. If hormonal therapy was started for local or distant failure, the patient's record was censored. Patients were sub-

grouped by race/ethnicity as white (non-Hispanic), African-American, Hispanic, or Asian. The patients' medical records were reviewed for serum PSA, Gleason score, clinical T stage, radiation dose, and age.

The initial evaluation had included a history, physical examination (including digital rectal examination), prostate-specific antigen (PSA) determination, and Gleason score determination (from needle biopsy or transurethral resection specimens). The initial PSA level and all available post-treatment PSA levels were extracted from the medical records. Bone scan, computed tomography of the abdomen/pelvis, magnetic resonance imaging of the abdomen/pelvis, chest radiography, and various blood studies had been performed as deemed necessary by the stage and initial evaluation protocol.

For this study, the clinical stage was retrospectively assigned based on data in the medical records according to the 1992 American Joint Committee on Cancer staging system.[15] Since the outcomes of the subgroups of patients with T1 tumors did not differ, T1a, T1b, and T1c were combined for our analysis. Similarly, all T2 tumors were combined for analysis. T3 and T4 tumors were combined because of the small number of patients with T4 tumors. Thus, a three-tier clinical stage grouping was used in this analysis (T1, T2, and T3/T4).

All pathology specimens were reviewed at the initial visit to M.D. Anderson, and a Gleason score was assigned in all except eight cases.

Radiotherapy Technique

During the study period, external-beam radiotherapy was administered via either a conventional

Table 1. Distribution of Study Variables by Race/Ethnicity[a]

Variable	Whites (n=810)	African Americans (n=86)	Hispanics (n=54)	Asians (n=14)	p Value[e]
Age					0.6634
<60 years	80 (10%)	12 (14%)	4 (7%)	2 (14%)	
60–64 years	137 (17%)	17 (20%)	9 (17%)	3 (21%)	
65–69 years	217 (27%)	17 (20%)	21 (39%)	0 (0%)	
70–74 years	264 (33%)	27 (31%)	12 (22%)	6 (43%)	
>74 years	112 (14%)	13 (15%)	8 (15%)	3 (21%)	
Initial PSA[b]					0.0012
0–4.0 ng/ml	141 (17%)	9 (10%)	6 (11%)	4 (29%)	
4.1–10.0 ng/ml	357 (44%)	32 (37%)	23 (43%)	3 (21%)	
10.1–20.0 ng/ml	220 (27%)	27 (31%)	13 (24%)	3 (21%)	
>20.0 ng/ml	89 (11%)	18 (21%)	12 (22%)	4 (29%)	
Gleason score[c]					0.0265
2–4	159 (20%)	11 (13%)	8 (15%)	0 (0%)	
5–7	556 (69%)	67 (78%)	37 (69%)	10 (71%)	
8–10	87 (11%)	8 (9%)	9 (17%)	4 (29%)	
Clinical T Stage[d]					0.2241
T1	290 (36%)	33 (38%)	14 (26%)	5 (36%)	
T2	408 (50%)	36 (42%)	29 (54%)	6 (43%)	
T3/T4	110 (14%)	17 (20%)	11 (20%)	3 (21%)	
Mean Radiation Dose (range)	68.69 Gy (60-78)	68.67 Gy (60-78)	68.88 Gy (62-78)	70.42 Gy (62-78)	0.5295
PSA Nadir					0.1041
0–0.5 ng/ml	390 (48%)	37 (43%)	18 (33%)	7 (50%)	
0.6–1.0 ng/ml	212 (26%)	29 (34%)	12 (22%)	3 (21%)	
1.1–1.5 ng/ml	98 (12%)	10 (12%)	9 (17%)	1 (7%)	
1.6–2.0 ng-ml	32 (4%)	5 (6%)	8 (15%)	1 (7%)	
>2.0 ng/ml	78 (10%)	5 (6%)	7 (13%)	2 (14%)	
Median Follow-Up	48 months	48 months	51 months	57 months	

[a] Data are numbers of patients unless otherwise specified; [b] Three patients missing initial PSA data; [c] Eight patients missing Gleason score data; [d] Seven patients missing clinical T stage data; [e] Statistical difference among various racial/ethnic groups

four-field approach or six-field conformal radiotherapy using three-dimensional treatment planning. Details of both the conventional and conformal techniques have been previously published.[14,16-18] Doses ranged from 64 to 78 Gy, with higher doses in more recently treated patients.

Clinical Follow-Up and Biochemical Failure

PSA was measured three months after completion of radiotherapy and every three-to-six months thereafter. Follow-up information was obtained from the patients' medical records or by contacting outside

Figure 1. (a) Actuarial biochemical disease-free survival curve for all 964 patients treated with external-beam radiotherapy for localized or locally advanced prostate cancer.

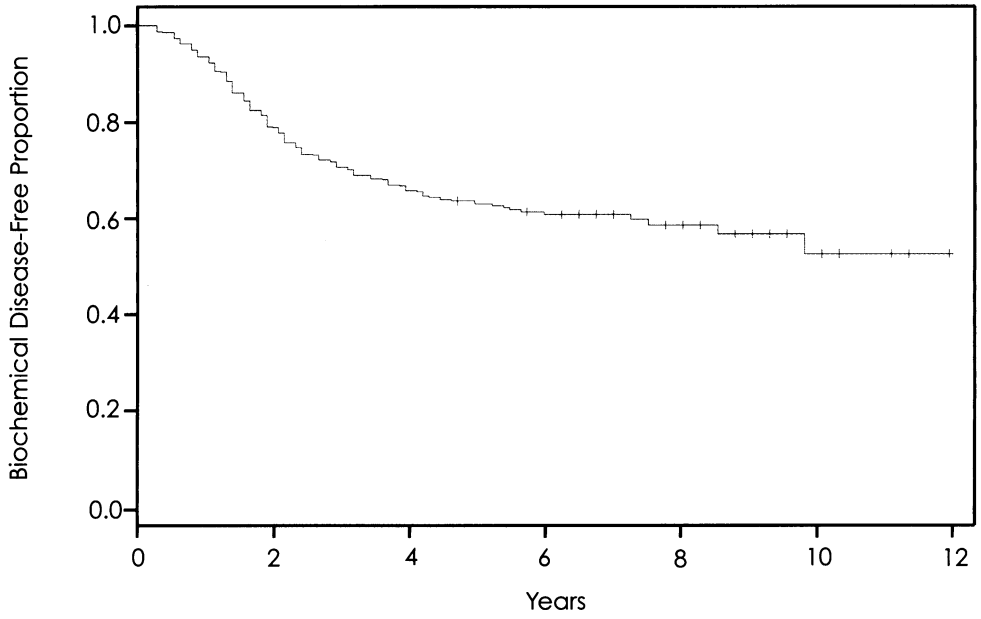
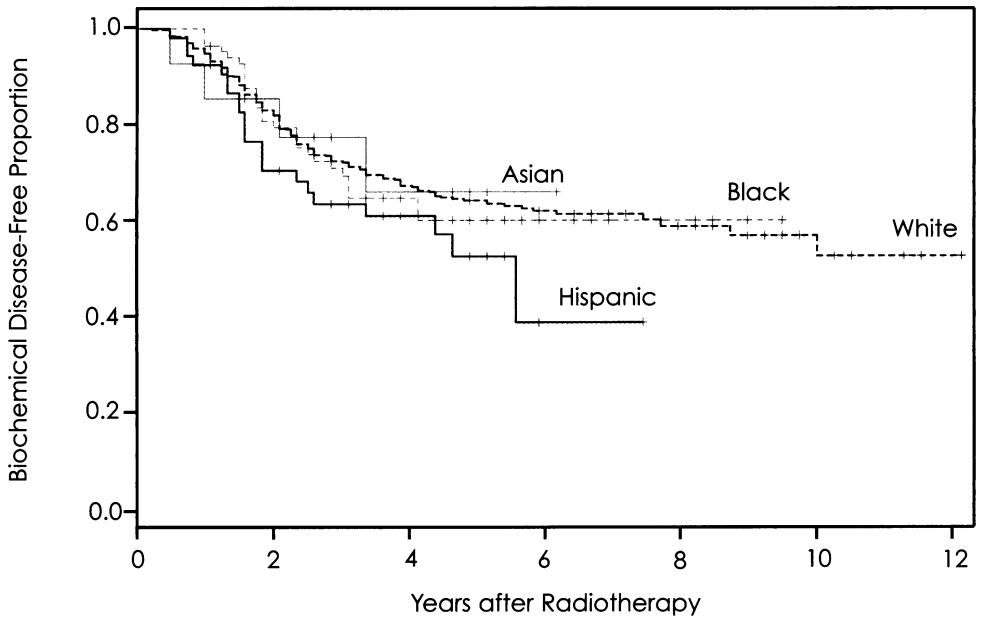


Figure 1. (b) Actuarial biochemical disease-free survival curves for each racial or ethnic group treated with external-beam radiotherapy for localized or locally advanced prostate cancer.



physicians/hospitals. All time intervals were calculated from the date of completion of radiotherapy. The American Society for Therapeutic Radiology and Oncology criterion for biochemical failure following radiotherapy—three consecutive increases in posttreatment PSA after achieving a nadir—was used to define biochemical failure.[19] The time to biochemical failure was midway between the posttreatment PSA nadir and the first of three consecutive rises in PSA.

Statistical Analysis

Differences in the distribution of demographic, clinical, and pathological variables between the various racial/ethnic groups were evaluated using Pearson's Chi-squared test. Biochemical disease-free survival rates were estimated by the life-table method and differences were evaluated using Pearson's Chi-squared test. Multivariate Cox regression analysis using the likelihood ratio test was done to evaluate the influence of clinical T stage, initial PSA, Gleason score, PSA nadir, age, radiation dose, and race/ethnicity on biochemical disease-free survival. The Jonckheere Terpstra test was used to assess patterns of clinical T stage, and Gleason score over time. A two-sided Pearson's Chi-squared test was used to compare differences in initial pretreatment PSA between 1995–1998 compared to the 1987–1994 time period. These differences were verified using Yates continuity correction. A p value <0.05 was considered statistically significant. The statistical analysis was performed using SAS version 6.12 software (SAS Institute, Cary, NC).

RESULTS

The clinical characteristics of the study group are shown in Table 1. Of the 964 patients in this series, 810 (84%) were white (non-Hispanic), and 154 (16%) were members of minority groups: 86 (9%) were African-American, 54 (6%) were Hispanic, and 14 (1%) were Asian. The median follow-up of the entire cohort was 48 months (range 12–142 months). There was no significant difference in the clinical T stage or radiation dose among racial/ethnic groups. Asians tended to present with disease at an older age (64% were ≥70 years). Furthermore, 29% of Asians presented with poorly differentiated prostate cancer (Gleason score of 8–10), compared to only 11% of whites. Seventeen percent of Hispanics also presented with Gleason scores of 8–10 (p=0.0265). The most significant difference in the pretreatment parameters was in the proportion of minorities who presented with PSA levels >20 ng/ml. More than 20% of men in all minority groups presented with a serum PSA >20 ng/ml, whereas only 11% of whites presented with a serum PSA >20 ng/ml (p=0.0012). Notably, 50% of Asians and 46% of Hispanics presented with a high initial PSA (>10 ng/ml).

Table 2 demonstrates the migration of clinical and pathologic factors from 1987–1998. When comparing the time intervals of 1995–1998 versus 1987-1994, the number of men presenting for external-beam radiotherapy with serum PSA levels <10 ng/ml increased to 74% from 57% for Caucasians (p <0.001), 71% from 40% for African Americans (p= 0.012), 67% from 49% for Hispanics (p=0.118), and no change (50%, p=0.893) for Asians. No dramatic

Table 2. Migration of Clinical and Pathologic

Variable	Number of Patients by Whites# 1987–1990 (n=193)	Whites# 1991–1994 (n=398)	Whites# 1995–1998 (n=217)	African Americans 1987–1990 (n=15)	African Americans 1991–1994 (n=50)
Serum PSA[b]					
0–4.0 ng/ml	63 (33%)	50 (13%)	28 (13%)	5 (33%)	4 (8%)
4.1–10.0 ng/ml	56 (29%)	168 (42%)	133 (61%)	2 (13%)	15 (30%)
10.1–20.0 ng/ml	42 (22%)	124 (31%)	52 (24%)	3 (20%)	20 (40%)
>20.0 ng/ml	30 (16%)	55 (14%)	4 (2%)	5 (33%)	11 (22%)
Gleason score[c]					
2–4	87 (45%)	64 (16%)	8 (4%)	5 (33%)	5 (10%)
5–7	93 (48%)	277 (70%)	184 (85%)	10 (67%)	39 (78%)
8–10	10 (5%)	56 (14%)	21 (10%)	0 (0%)	6 (12%)
Clinical T stage[d]					
T1	75 (39%)	121 (30%)	94 (43%)	7 (47%)	17 (34%)
T2	99 (51%)	210 (53%)	99 (46%)	6 (40%)	21 (42%)
T3	19 (10%)	65 (16%)	24 (11%)	2 (13%)	12 (24%)
T4	0 (0%)	2 (1%)	0 (0%)	0 (0%)	0 (0%)

[a] Data are numbers of patients (%); [b] Three patients missing initial PSA data; [c] Eight patients missing Gleason score data;

change was seen in the clinical T stage at presentation among any of the four groups over time. However, there was an overall reduction in the proportion of Gleason 2–4 tumors over time.

Using logistic regression analysis of PSA nadir values after treatment, we noted one significant difference between the racial groups. Hispanic patients failed to reach a PSA nadir of ≤1 ng/ml significantly more often than did the other patient cohorts (44% versus 23–29%, p=0.0214).

Figure 1a shows the actuarial biochemical disease-free survival curve for the entire study group. The one-, five-, and 10-year biochemical disease-free survival rates were 92%, 62%, and 58%, respectively. Figure 1b illustrates the biochemical disease-free survival curves for each racial or ethnic group. There were no statistically significant differences in disease-free survival among whites, African Americans, and Asians. However, Hispanics tended to have a lower five-year biochemical disease-free survival rate (52%) than did whites (65%; p=0.077; risk ratio 1.44, 95% confidence interval = 0.87–1.21). Multivariate regression with backward elimination of variables demonstrated that initial PSA >10.0 ng/ml, Gleason score >7, and lower radiation doses were predictive of biochemical failure in all groups (data not shown).

DISCUSSION

Our study provides evidence that Hispanics, as previously reported for African Americans, tend to present with higher initial PSA levels. This is consistent with a study by Hoffman et al. who reported that 23% of Hispanics presented with an initial PSA >20 ng/ml, compared to only 16% of whites.[20] In our study, Hispanic patients also tended to present with higher Gleason scores. The higher percentage of Hispanic patients with unfavorable disease characteristics may have contributed to the higher percentage with PSA nadirs >1 ng/ml. Even after accounting for differences in prognostic parameters, Hispanics were noted to have a poorer five-year biochemical disease-free survival rate of 52%, compared to 65% in white patients, which was almost statistically significant. The difference in survival between Hispanics and other racial/ethnic groups was not explained by differences in follow-up, as previously reported by Vicini et al.,[21] since the median follow-up of Hispanics was 51 months and the median follow-up of both whites and African Americans was 48 months.

Asian men presented in our cohort with higher-grade tumors and higher serum PSA values. Similarly, Young et al. previously reported that of 51 Asian men treated with external-beam radiotherapy, 19% had Gleason[8-10] disease, compared to only 7% of white men.[22] Young et al did not note a difference in serum PSA at presentation.[22] Even though Asians in our study presented with high-risk features, they did not demonstrate an increased risk of biochemical failure. The explanation for this is unknown. However, given the small size of the Asian cohort in our study, the data must be interpreted with caution.

It was previously shown that African-American men with prostate cancer presented with more advanced disease than did white American men.[2,4,5,7-

Factors from 1987–1998.[a]

Ethnicity and Period	Hispanics			Asians		
1995–1998 (n=21)	1987–1990 (n=8)	1991–1994 (n=31)	1995–1998 (n=15)	1987–1990 (n=2)	1991–1994 (n=6)	1995–1998 (n=6)
0 (0%)	0 (0%)	3 (10%)	3 (20%)	1 (50%)	3 (50%)	0 (0%)
15 (71%)	3 (38%)	13 (42%)	7 (47%)	0 (0%)	0 (0%)	3 (50%)
4 (19%)	2 (24%)	6 (19%)	5 (33%)	0 (0%)	1 (17%)	2 (33%)
2 (10%)	3 (38%)	9 (29)	0 (0%)	1 (50%)	2 (33%)	1 (17%)
1 (5%)	4 (50%)	3 (10%)	1 (7%)	0 (0%)	0 (0%)	0 (0%)
18 (85%)	4 (50%)	23 (74%)	10 (67%)	2 (100%)	5 (83%)	3 (50%)
2 (10%)	0 (0%)	5 (16%)	4 (27%)	0 (0%)	1 (17%)	3 (50%)
9 (43%)	2 (25%)	8 (26%)	4 (27%)	1 (50%)	3 (50%)	1 (17%)
9 (43%)	5 (63%)	16 (52%)	8 (53%)	1 (50%)	2 (33%)	3 (50%)
3 (14%)	1 (12%)	6 (19%)	3 (20%)	0 (0%)	1 (17%)	2 (33%)
0 (0%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

[a] Seven patients missing clinical T stage data.

[12,20,22-24] Pettaway et al. reported on the radical prostatectomy specimens of 40 black patients compared to 148 white patients. They found that black patients presented with a higher initial PSA and exhibited a significantly higher incidence of seminal vesicle involvement and cancers with a Gleason score of 8 or more.[25] Similarly, we were able to demonstrate that African Americans presented with a serum PSA >20 ng/ml more often than did whites. Other reports have also demonstrated that initial serum PSA levels were different between African Americans and whites.[6,14,26] Considering the known relationship between increasing serum PSA levels and tumor volume,[25] our data are consistent with the hypothesis that African-American, Hispanic, and Asian patients presented with larger tumors compared to white males.

However, the number of white, African-American, and Hispanic men presenting for external-beam radiotherapy with PSA levels <10 ng/ml increased over the time period of 1995–1998 compared to the period from 1987–1994. Thus, the number of African-American patients presenting with favorable characteristics (PSA <10 ng/ml) is increasing. These findings suggest that the message of screening and early detection may be reaching the African-American community. Godley et al. recently reported higher mortality for African-American patients compared to white patients.[27] It is likely that the improved clinical features seen in minority patients now may translate in the future to equal survival outcomes for all races. Continued diligence in screening and early detection may improve prostate cancer outcome for other minority populations.

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